Fetal Development as Vulnerable Periods
*When does the fetal period begin?

1. 6 weeks
2. 9 weeks
3. 10 weeks
4. 16 weeks

*Add 2 weeks if calculating from the last menstrual cycle
6 weeks
11-12 Weeks
18 Weeks
Risk of Birth Defects Being Induced

- Increasing Risk
- Weeks Gestation
  - 0
  - 3
  - 5
  - 8
  - 38
  - Embryonic Period
  - Fetal Period
  - First Prenatal Visit
  - Parturition

**3rd Wk**
- **Imp 5**
- **5th Wk**
  - **Imp 5**
  - **Imp 6**
  - **Imp 7**
  - **Imp 8**
  - **Imp 9**
  - **Imp 10**
  - **Imp 11**
  - **Imp 12**

ANY MALFORMATION
- 17%

MICROPHTHALMIA
- 20%

SITUS INVERSUS
- 98%

FORELIMB SHORT
- 98%

HINDLIMB SHORT
- 100%

FOOT DIGIT MALFORMATION
- 100%

CLEFT PALATE
- 82%

5wk
6wk
5-6wk
7-8wk

3wk
4wk


**3rd Wk**
- **Imp 5**
- **5th Wk**
  - **Imp 5**
  - **Imp 6**
  - **Imp 7**
  - **Imp 8**
  - **Imp 9**
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3wk
4wk
Teratogenicity of Rubella Infection

Prior to 8 weeks: 100% of infected infants had heart defects and/or deafness.

At 11-14 weeks: 35% of infected infants had deafness and none had heart defects.
Thalidomide and Birth Defects

Forelimbs if started the drug in the 4th week

Hindlimbs if started the drug in the 5th week

...But thalidomide also caused heart defects, ear defects, and GI tract defects!
End of 2nd week

Beginning of 3rd week
Heart Development late 3\textsuperscript{rd} and early 4\textsuperscript{th} weeks
Cells in the primary heart field (PHF) are specified to pattern the heart
Heart Development late 3rd and early 4th weeks
Secondary heart field

4th week

End of 4th week
Atrial and Ventricular Septa Formation: 5th and 6th weeks
Septum formation in the outflow tract: 4th to 8th weeks

Fusion occurs in the 6th-8th weeks

Neural crest cells

4th week

22q11.1 deletion (Di George) syndrome
Face and heart defects
### Congenital Heart Defects Are Heterogeneous in Origin & Occur during the (3rd-7th weeks)

<table>
<thead>
<tr>
<th>Target Tissue</th>
<th>Cell Process</th>
<th>Normal Effect</th>
<th>Birth Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Progenitor cells (Primary Heart Field [PHF])</td>
<td>Laterality &amp; patterning (Week 3)</td>
<td>Specification of the outflow tract ventricles &amp; atria</td>
<td>DORV, TGA, I-TGA, ASD, VSD, atrial isomerism, ventricular inversion, dextrocardia &amp; common truncus arteriosus</td>
</tr>
<tr>
<td>Heart tube</td>
<td>Extracellular matrix (Weeks 3&amp;4)</td>
<td>Looping</td>
<td>Dextrocardia</td>
</tr>
<tr>
<td>Atrioventricular endocardial cushions</td>
<td>Cell proliferation &amp; migration (Week 5)</td>
<td>Division of the AV canal; Formation of the AV valves; Formation of the membranous IVS</td>
<td>VSDs, ASDs, mitral insufficiency, tricuspid atresia, positioning &amp; leaflet defects</td>
</tr>
<tr>
<td>Secondary heart field (SHF)</td>
<td>cell proliferation, migration &amp; viability (Week 4)</td>
<td>Lengthening, positioning and division of the outflow tract</td>
<td>Tetralogy of Fallot, pulmonary stenosis &amp; atresia, TGA, DORV</td>
</tr>
<tr>
<td>Outflow tract (Conotruncus)</td>
<td>Neural crest cell proliferation, migration &amp; viability (Weeks 4-7)</td>
<td>Formation of the conotruncal endocardial cushions</td>
<td>Common truncus arteriosus</td>
</tr>
</tbody>
</table>
When it comes to development, timing is everything!

- The **embryonic** period (3rd to 8\textsuperscript{th} weeks) is the most sensitive time for causing structural birth defects.

- The **fetal** period (9\textsuperscript{th} week to birth) is not very sensitive to teratogen induced birth defects, although some organs remain at risk, especially the brain.

- Some organs will be susceptible for long periods (the heart), others for shorter periods (the forelimb).

- Not every organ will have the same sensitivity to a given concentration of a teratogen, but primordial cells and stages will be more susceptible than later stages (primordial heart and neural crest cells).

- Multiple organs may be “hit” at the same time, sometimes resulting in the characteristics of a syndrome.
Why is Preconception care the way to prevent birth defects?

See Below!